7th POSTGRADUATE
Lymphoma
Conference

Hodgkin Lymphoma: Finally CAR-T?

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President:
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Disclosures

Disclosures of Carlos A. Ramos

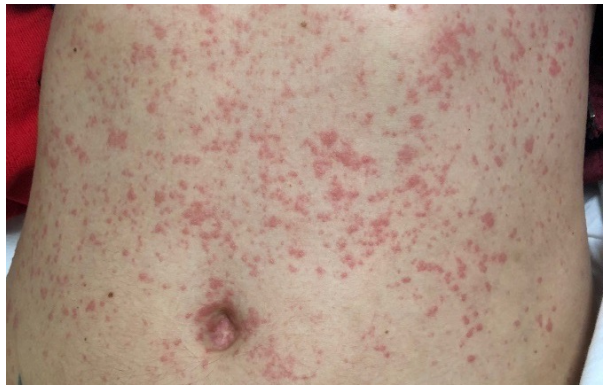
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis						✓	
Genentech			✓				
Tessa Therapeutics	✓						✓
Athenex, Inc.	✓						
CRISPR Therapeutics			✓				

Targeting CD30 with a CAR

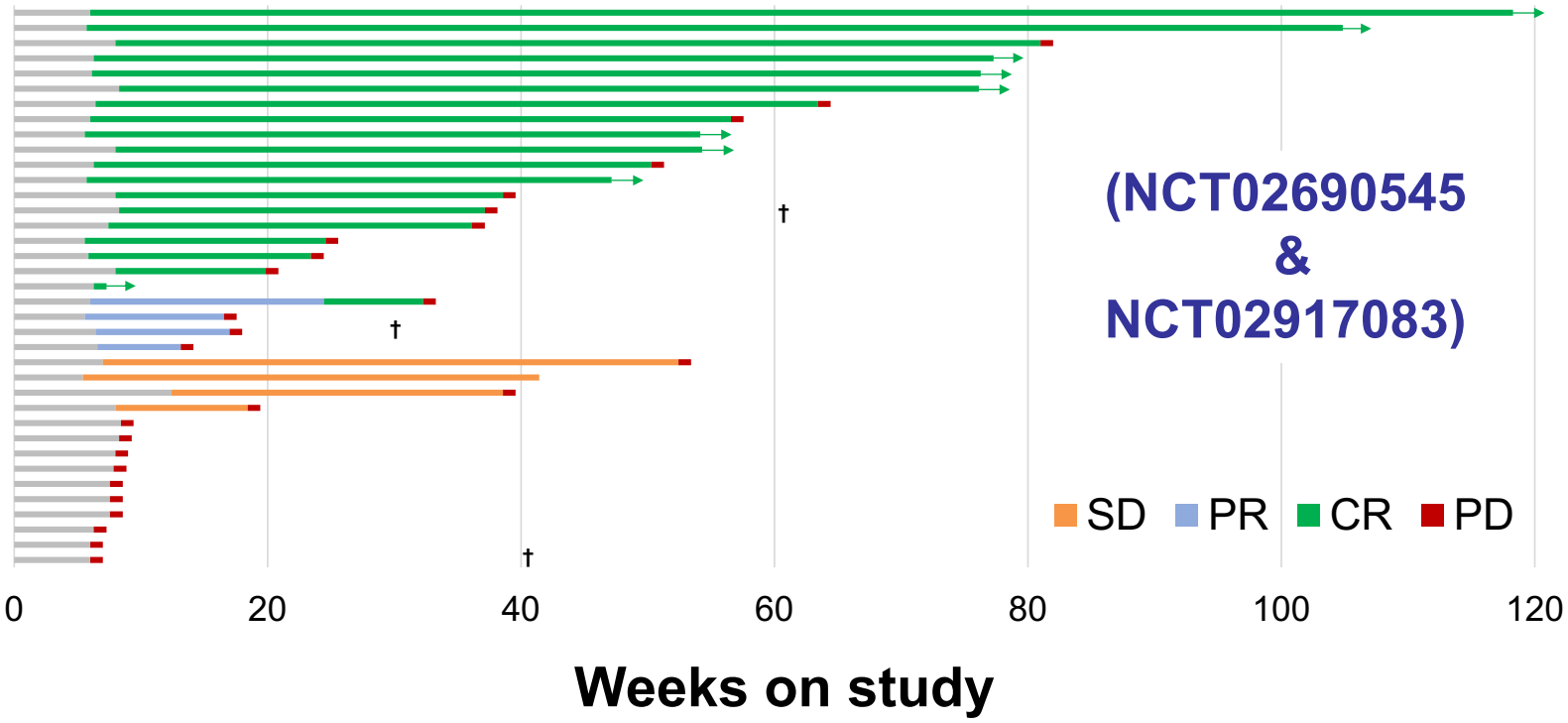
- CD19-specific (and BCMA) CAR-T cells are highly successful against B-cell NHL and ALL (and myeloma)
- Adequate targets for other disorders have been more difficult to define
- CD30 has been validated as an immune target (e.g. brentuximab vedotin)
- A CD30-specific CAR (CD30.CAR) has activity in pre-clinical models of HL (Hombach, Ca Res 1998; Savoldo, Blood 2007)

Autologous CD30.CAR-T cells in HL (BCM/UNC)

- CRS in 10/42 pts
  - all grade 1
  - all resolved spontaneously
- No neurotoxicity
- Chemo related cytopenias
- Rash in 20/42 pts



- With optimal lymphodepletion:
  - 72% overall response rate
  - 59% complete responses



(Ramos, Grover *et al.*, J Clin Oncol 2020)

Autologous CD30.CAR-T cells in HL (multicenter)

Response Assessments (N = 14)		By IRRC N (%)	By Investigators N (%)
ORR (CR+PR)		10 (71.4)	13 (92.9)
Best Overall Response	CR	8 (57.1)	6 (42.9)
	PR	2 (14.3)	7 (50.0)
	SD	1 (7.1)	1 (7.1)
	PD	3 (21.4)	0 (0)

(NCT04268706)

(data courtesy of Ivan Horak, Tessa Therapeutics, ASH 2021)

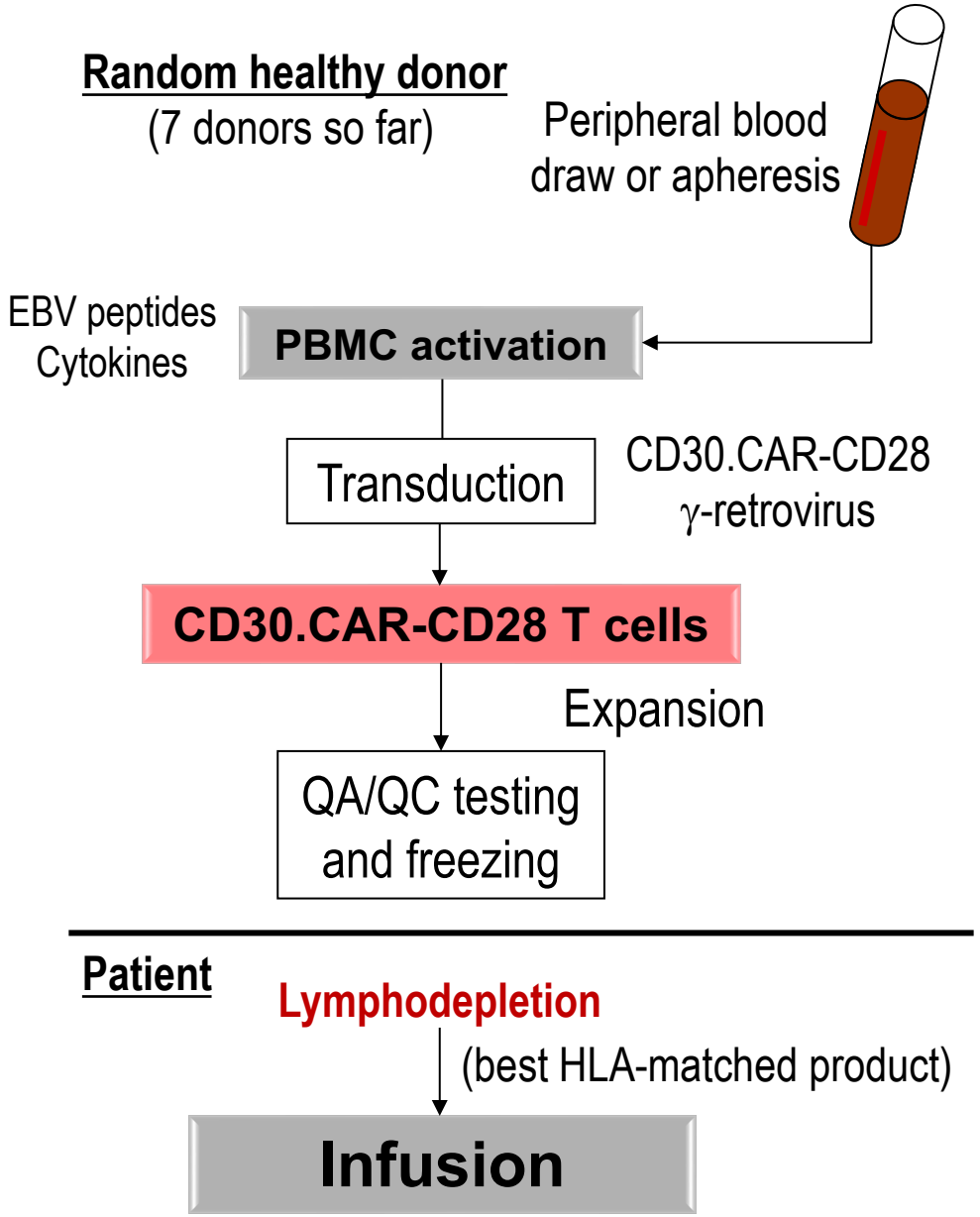
Limitations of Autologous CAR-T Cells

- Manufacture of individual patient-derived CAR T-cells
  - too time consuming to benefit acutely ill patients
  - prior chemotherapy exposure may result in suboptimal product
  - difficult to scale for large numbers of patients, expensive
- "Off-the-shelf" immune effector products that are banked from healthy donors would improve accessibility, allow rapid treatment, and reduce costs
  - need to avoid consequences of alloreactivity
    - Graft-versus-host disease (GVHD) and CAR-T cell rejection

Allogeneic CD30.CAR-EBVSTs

- Avoid GVHD and may be protected from rejection
- Allogeneic EBV-specific T cells are safe in HSCT and non-HSCT recipients (Heslop, Sharma, Rooney, JCO 2021)
  - Many patients treated in several trials without GVHD
  - Proliferate in patients, possess memory and have potential to persist
  - Can localize to lymphoid tissues and sites of inflammation
- Activated T cells express CD30
  - Recipient T cells reacting against donor CAR-T cells may be killed by CD30.CAR-T cells

BESTA Clinical Trial (NCT04288726)



- Phase 1 trial
- $CD30^+$ malignancies
  - Active disease
  - Failure of standard treatment
- Dose escalation (BOIN method)
  - 40, 100, 400, 800×10^6 CAR^+ cells
- Lymphodepleting chemotherapy
  - Cyclophosphamide + fludarabine
- Primary objective: safety
- Secondary: response per Lugano
  - Initial assessment at week 4-6

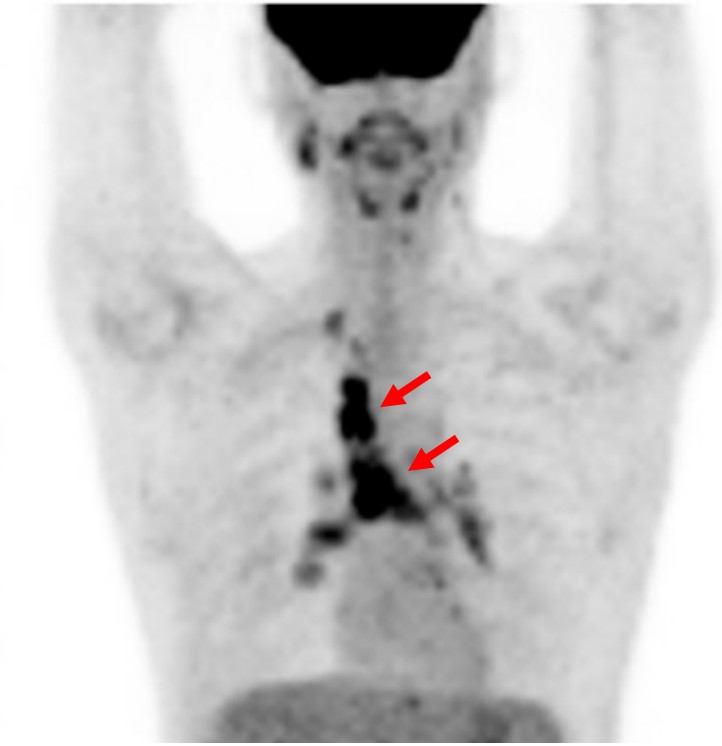
Patient Characteristics

Patient	Age	Sex	Disease	# Prior Rx	Prior Treatments (Rx)
#1	34	F	Hodgkin lymphoma (NS)	5	ABVD, ICE, HDT/ASCT, brentuximab vedotin (BV), nivolumab
#2	47	M	Hodgkin lymphoma (MC)	5	ABVD, ESHAP, HDT/ASCT, BV, pembrolizumab
#3	29	M	Hodgkin lymphoma (NS)	6	ABVD, ICE, HDT/ASCT, BV, nivolumab, BV+bendamustine
#4	53	M	Hodgkin lymphoma (NS)	5	ABVD+COPP, BV, nivolumab, everolimus, bendamustine
#5	39	F	Hodgkin lymphoma (NS)	3	ABVD, nivolumab, BV+nivolumab
#6	37	M	Hodgkin lymphoma (NS)	4	ABVD+XRT, ICE, HDT/ASCT, BV
#7	29	F	Hodgkin lymphoma (NS)	5	ABVD, BV-ICE, HDT/ASCT, BV, bendamustine+gemcitabine+nivolumab
#8	44	F	Hodgkin lymphoma (NS)	6	ABVD, ICE, BV, BV+bendamustine, HDT/ASCT, pembrolizumab
#9 (#1)	35	F	Hodgkin lymphoma (NS)	7	ABVD, ICE, HDT/ASCT, BV, nivolumab, gemcitabine, BESTA
#10	24	F	Hodgkin lymphoma (NS)	4	ABVD, ICE, BV+nivolumab, everolimus+itacitinib
#11 (#6)	37	M	Hodgkin lymphoma (NS)	5	ABVD+XRT, ICE, HDT/ASCT, BV, BESTA
#12	35	F	Composite lymphoma	5	R-CHOP, XRT, BV-ICE, BV+nivolumab, pembro+vinorelbine+lipos doxor
#13	42	F	Hodgkin lymphoma (NS)	3	BV-AVD, pembrolizumab, bendamustine
#14	22	M	Hodgkin lymphoma (NS)	4	ABVD, ICE, BV+nivolumab, nivolumab
#15	24	M	Hodgkin lymphoma (MC)	3	ABVD, BV-ICE, HDT/ASCT
#16	37	M	Hodgkin lymphoma (NS)	6	ABVD, ICE, BV, nivolumab, BV+bendamustine, pembrolizumab

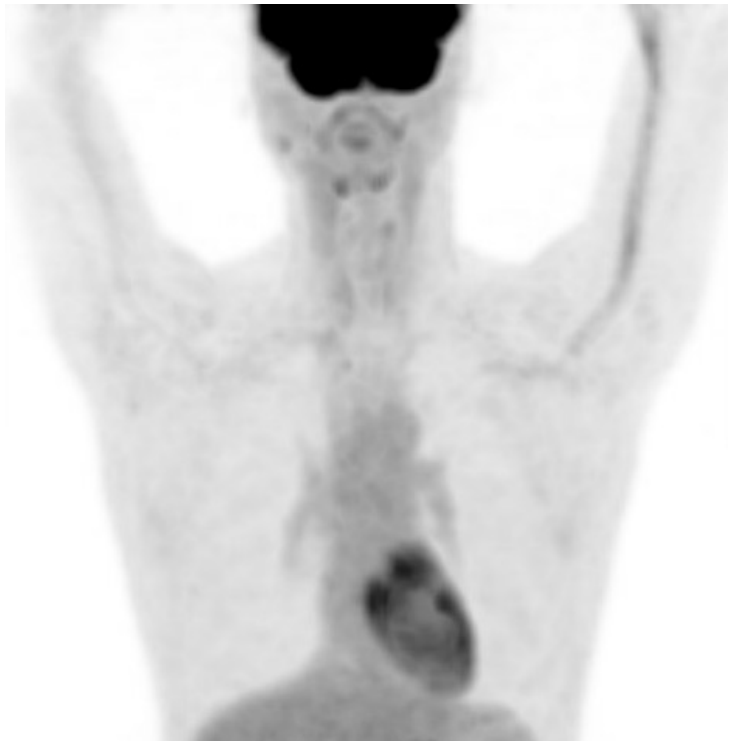
Clinical Response to CAR-EBVSTs (pt #6)

- 37 y.o. male with relapsed Hodgkin lymphoma
- Dose level 2
- Complete remission

Pre-infusion



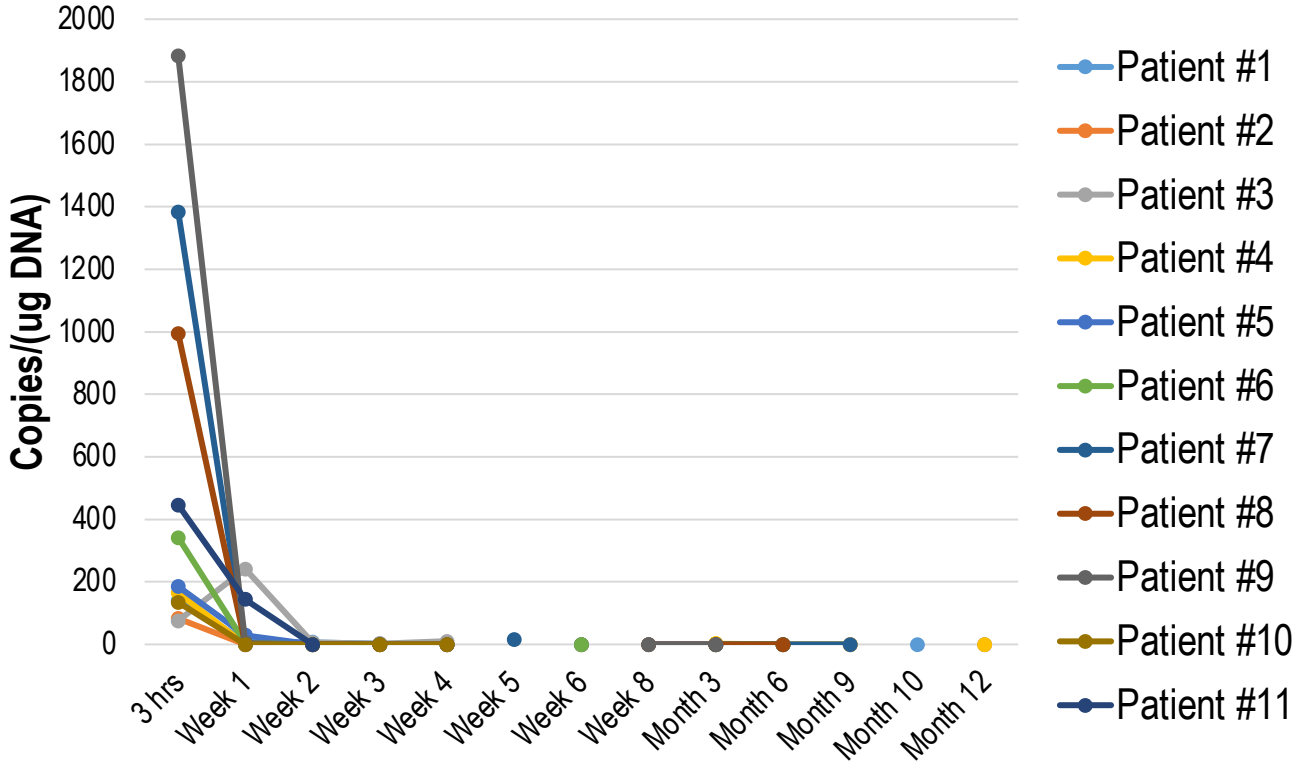
Week 6

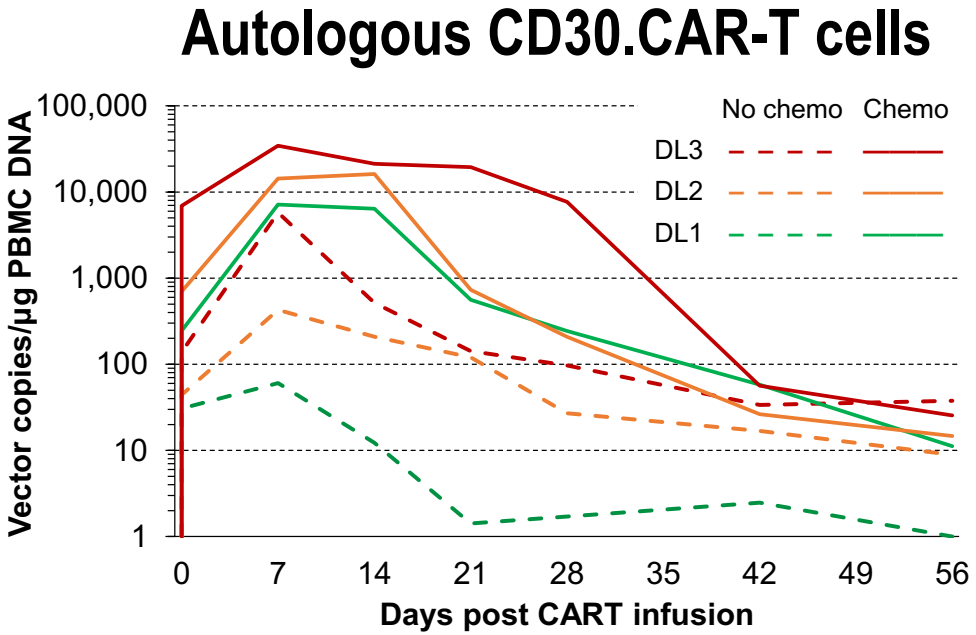


Safety and Response Data

Patient	Dose	Line	HLA I, II match	CRS	Unexpected SAE	Best Clinical Response
#1	40×10^6	#3	3,2	None	None	Partial response
#2	40×10^6	#3	2,0	None	None	Partial response
#3	40×10^6	#3	1,1	None	None	Progressive disease
#4	100×10^6	#5	1,1	None	None	Progressive disease
#5	100×10^6	#1	1,1	None	None	Partial response
#6	100×10^6	#2	1,0	None	None	Complete Response
#7	400×10^6	#1	2,2	None	Prolonged pancytopenia	Complete Response
#8	400×10^6	#3	2,1	None	None	Complete Response
#9 (#1)	400×10^6	#3	3,2	Grade 1	Prolonged pancytopenia	Complete Response
#10	400×10^6	#1	1,0	Grade 1	None	Partial response
#11 (#6)	400×10^6	#2	1,0	None	None	Complete Response
#12	400×10^6	#4	3,2	Grade 1	None	Progressive disease
#13	400×10^6	#3	2,0	Grade 1	None	Partial response
#14	400×10^6	#6	2,2	None	None	Complete Response
#15	400×10^6	#3	2,0	None	None	Progressive disease
#16	800×10^6	#4	4,3	Grade 1	None	Partial response

Allogeneic CD30.CAR-EBVSTs Have Limited Persistence in Peripheral Blood

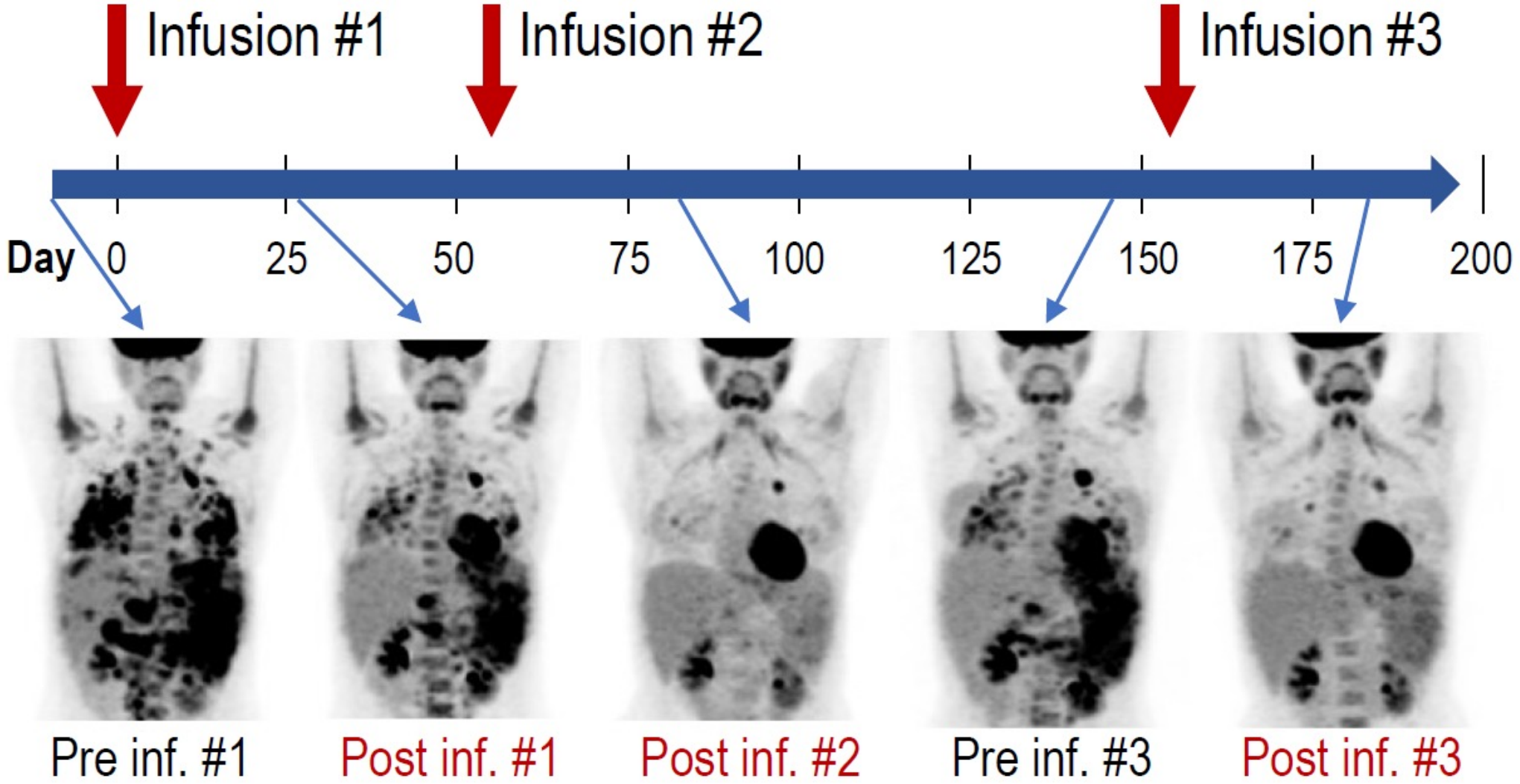




Ramos CA, *et al.* JCI (2017) & JCO (2020)

- CD30.CAR transgene detected with real time qPCR
- Most patients show rapid loss of CD30.CAR EBVSTs in blood
- Autologous CD30.CAR-T cells show longer persistence

Repeat Infusions Are Effective (pt #10)



Conclusions

- Adoptive transfer of autologous and allogeneic CD30.CAR-T cells is feasible and safe
- Both autologous and allogeneic CD30.CAR-T cells lead to clinical responses:
  - CD30.CAR EBVSTs lack persistence in blood but are not limited by rejection, as additional infusions are effective
  - CAR-EBVSTs are a promising platform for “off-the-shelf” cancer immunotherapy
- But finally CAR-T? Maybe…
  - Cellular immune therapy seems to work for HL but…
  - Industry? Academia? Hybrid model?

Grazie!

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